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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Guenther, Catherine	Examiner:	Wilson, Michael C.
Serial No.:	09/883,093	Group Art Unit:	1632
Filed:	June 14, 2001	Docket No.:	R126/75658.241
Confirmation No.:	7936		
Title:	Transgenic Mice Containing Nuclear Hormone Receptor Gene Disruptions		

DECLARATION OF JOHN BURKE PURSUANT TO 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, John E. Burke, residing at 16357 E. Berry Avenue, Centennial CO 80015, hereby declare:

1. I am currently, and have been since 1998, the Attorney of Record for the Applicant and Assignee, Deltagen, Inc. I am listed on the originally filed Power of Attorney for the present application. From December 1996 to December 1999, I was Of Counsel with the law firm of Pillsbury Madison & Sutro (currently Pillsbury Winthrop) where I represented Deltagen with respect to intellectual property matters, including patent matters relating to their transgenic mouse program. From December 1999 until December 2001, I served as Deltagen's Vice President of Intellectual Property, where I supervised Deltagen's internal patent department. All of the applications, including the present application, covering the 750 lines of mice in DeltaBase were drafted by Deltagen's patent department. From December 2001 until April 2003, I served as Deltagen's Senior Vice President and General Counsel. From April 2003 through April 2005, I was a partner with the Denver office of Merchant & Gould, where I continued to represent Deltagen with regard to intellectual matters, including patent matters. I am presently employed as a Shareholder with the Denver office of the law firm of Greenberg Traurig, where I am

responsible for prosecution of Deltagens's patent portfolio relating to their transgenic mice program, including the present application.

2. I am familiar with the present application. I am familiar with the Final Office Action mailed October 6, 2005. I am aware that the Examiner has rejected the claims, in part, for allegedly failing to meet the utility and enablement requirements. I am aware that the Examiner has argued that the specification does not disclose what generation mice were used or what wild-type controls were used in the phenotypic analyses.

3. I hereby declare that, as evidenced by the attached Exhibit, the subject matter of the present application, mCAR2 gene knockout mice, were compared with control mice of identical background.

4. I hereby declare that the claimed mCAR2 gene knockout mouse has been extensively analyzed using the tests set forth in the Examples. This data has been incorporated into Deltagen's commercial database product, DeltaBase.

5. I hereby declare that I have accessed Deltagen's internal web-based DeltaBase database to review the data derived from analyses of the claimed mice. I hereby declare that the attached Exhibit contains three (3) pages, representing screen printouts from DeltaBase.

6. Exhibit pages 1 and 2 represent a series of screen shots of the Histopathology Summary for the mCAR2 gene. As shown, the mCAR2 gene has been internally designated as Gene 126. The Accession number is referred to at the top of the page (AF009328). According to the Summary, changes that may be related to genotype include lymphoid depletion of the thymus. The Summary further notes that the "changes seen in the thymuses of affected animals are suggestive of thymic dysplasia; however, severe atrophy cannot be ruled out."

7. Exhibit page 3 shows the raw histopathology data, and more specifically, the recorded observations for the thymus. Column 1 indicates the gene number 126; column 2 indicates the

ES cell line 200; column 3 indicates the genotype; column 4 indicates the sex of the subject mouse and column 6 indicates the mouse ID number. All of the mice are of the same generation, F2N0. Thus, the homozygous (-/-), heterozygous (+/-) and wild type mice (+/+) were derived from the same ES cell line, and are of the same F and N generation. Thus, the mice were compared with mice of the same background.

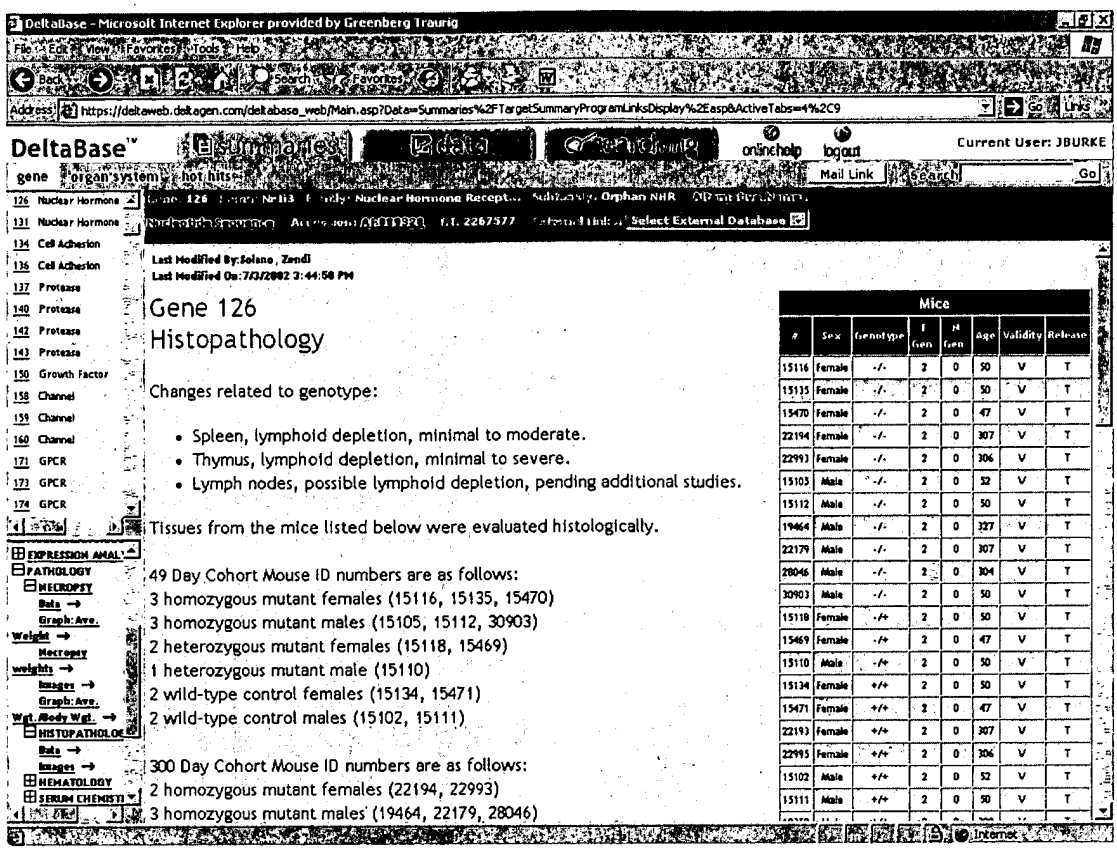
8. I further declare that all statements made herein of my own knowledge are true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

JER

John E. Burke, Reg. No. 35,836

3-30-06

Date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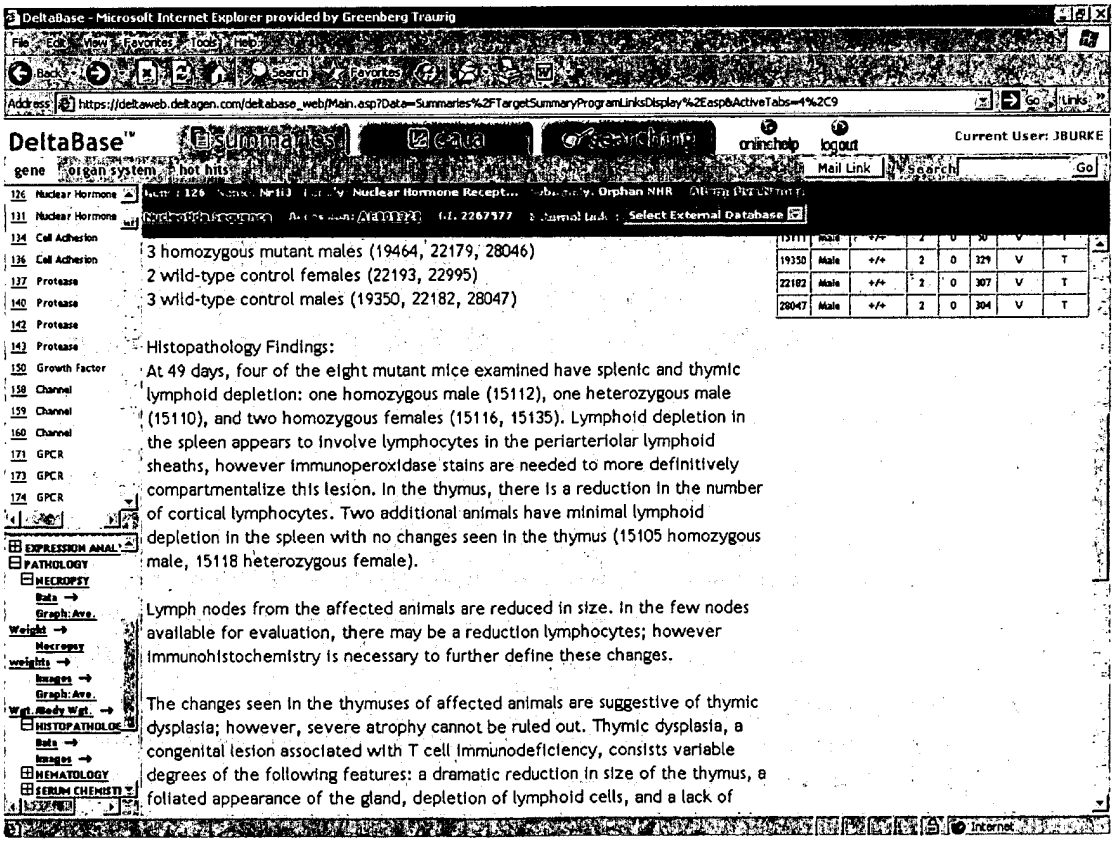
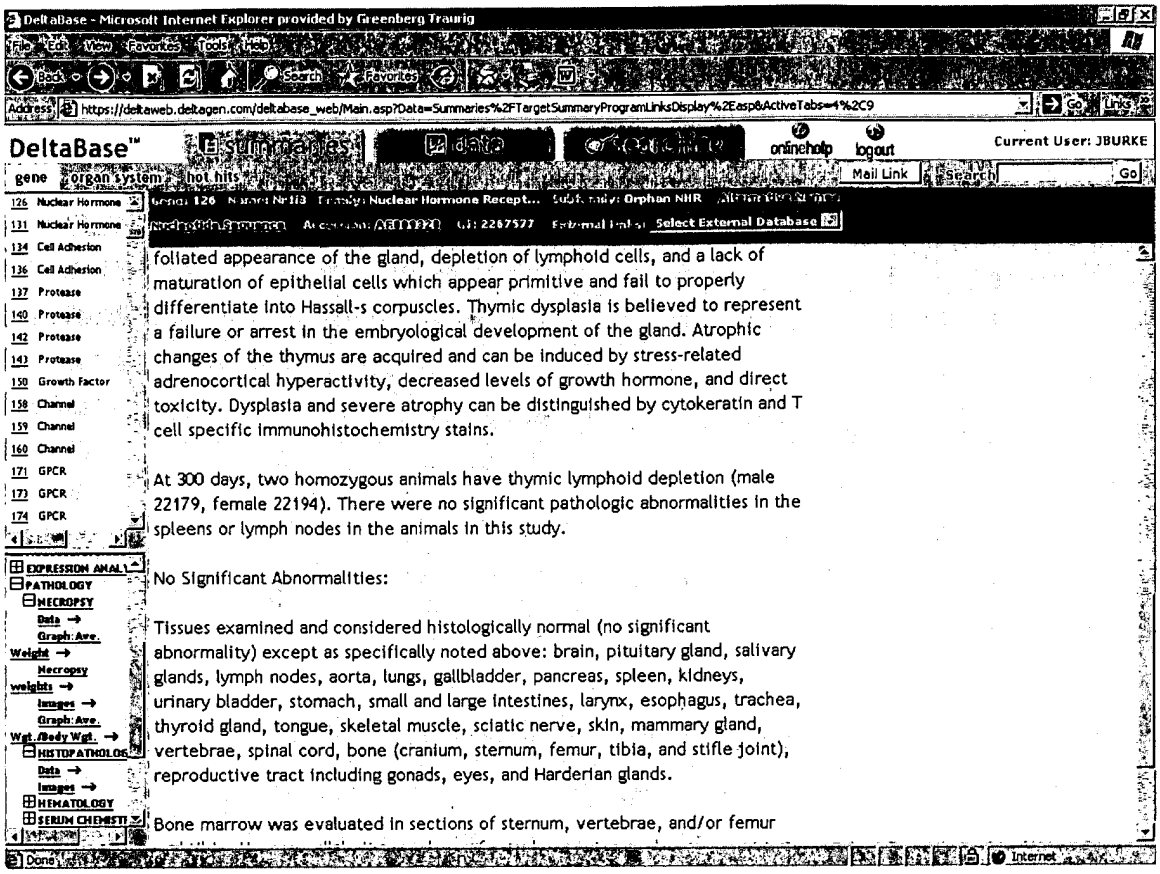
Gene 126
Histopathology
Changes related to genotype:
• Spleen, lymphoid depletion, minimal to moderate.
• Thymus, lymphoid depletion, minimal to severe.
• Lymph nodes, possible lymphoid depletion, pending additional studies.
Tissues from the mice listed below were evaluated histologically.
49 Day Cohort Mouse ID numbers are as follows:
3 homozygous mutant females (15116, 15135, 15470)
3 homozygous mutant males (15105, 15112, 30903)
2 heterozygous mutant females (15118, 15469)
1 heterozygous mutant male (15110)
2 wild-type control females (15134, 15471)
2 wild-type control males (15102, 15111)
300 Day Cohort Mouse ID numbers are as follows:
2 homozygous mutant females (22194, 22993)
3 homozygous mutant males (19464, 22179, 28046)
Mice
Sex Genotype F Gen N Gen Age Validity Release
15116 Female -/- 2 0 50 V T
15135 Female -/- 2 0 50 V T
15470 Female -/- 2 0 47 V T
22194 Female -/- 2 0 307 V T
22993 Female -/- 2 0 306 V T
15105 Male -/- 2 0 52 V T
15112 Male -/- 2 0 50 V T
19464 Male -/- 2 0 327 V T
22179 Male -/- 2 0 307 V T
28046 Male -/- 2 0 304 V T
30903 Male -/- 2 0 50 V T
15118 Female -/+ 2 0 50 V T
15469 Female -/+ 2 0 47 V T
15110 Male -/+ 2 0 50 V T
15134 Female +/+ 2 0 50 V T
15471 Female +/+ 2 0 47 V T
22193 Female +/+ 2 0 307 V T
22995 Female +/+ 2 0 306 V T
15102 Male +/+ 2 0 52 V T
15111 Male +/+ 2 0 50 V T


DeltaBase - Microsoft Internet Explorer provided by Greenberg Traurig
DeltaBase™
Summaries
Data
Searching
Current User: JBURKE
3 homozygous mutant males (19464, 22179, 28046)
2 wild-type control females (22193, 22995)
3 wild-type control males (19350, 22182, 28047)
Histopathology Findings:
At 49 days, four of the eight mutant mice examined have splenic and thymic lymphoid depletion: one homozygous male (15112), one heterozygous male (15110), and two homozygous females (15116, 15135). Lymphoid depletion in the spleen appears to involve lymphocytes in the periarteriolar lymphoid sheaths, however immunoperoxidase stains are needed to more definitively compartmentalize this lesion. In the thymus, there is a reduction in the number of cortical lymphocytes. Two additional animals have minimal lymphoid depletion in the spleen with no changes seen in the thymus (15105 homozygous male, 15118 heterozygous female).
Lymph nodes from the affected animals are reduced in size. In the few nodes available for evaluation, there may be a reduction lymphocytes; however immunohistochemistry is necessary to further define these changes.
The changes seen in the thymuses of affected animals are suggestive of thymic dysplasia; however, severe atrophy cannot be ruled out. Thymic dysplasia, a congenital lesion associated with T cell immunodeficiency, consists variable degrees of the following features: a dramatic reduction in size of the thymus, a foliated appearance of the gland, depletion of lymphoid cells, and a lack of
19350 Male +/+ 2 0 329 V T
22182 Male +/+ 2 0 307 V T
28047 Male +/+ 2 0 304 V T



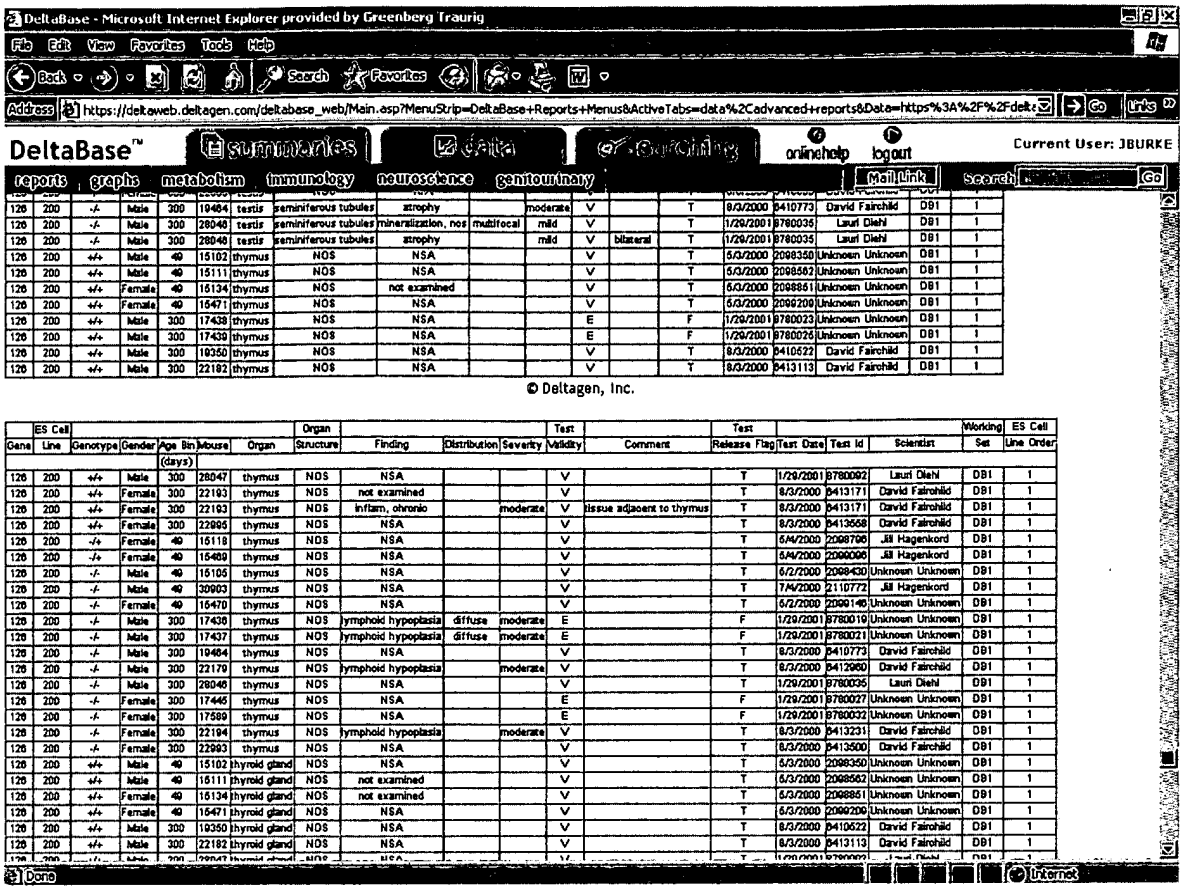
foliated appearance of the gland, depletion of lymphoid cells, and a lack of maturation of epithelial cells which appear primitive and fail to properly differentiate into Hassall-s corpuscles. Thymic dysplasia is believed to represent a failure or arrest in the embryological development of the gland. Atrophic changes of the thymus are acquired and can be induced by stress-related adrenocortical hyperactivity, decreased levels of growth hormone, and direct toxicity. Dysplasia and severe atrophy can be distinguished by cytokeratin and T cell specific immunohistochemistry stains.

At 300 days, two homozygous animals have thymic lymphoid depletion (male 22179, female 22194). There were no significant pathologic abnormalities in the spleens or lymph nodes in the animals in this study.

No Significant Abnormalities:

Tissues examined and considered histologically normal (no significant abnormality) except as specifically noted above: brain, pituitary gland, salivary glands, lymph nodes, aorta, lungs, gallbladder, pancreas, spleen, kidneys, urinary bladder, stomach, small and large intestines, larynx, esophagus, trachea, thyroid gland, tongue, skeletal muscle, sciatic nerve, skin, mammary gland, vertebrae, spinal cord, bone (cranium, sternum, femur, tibia, and stifle joint), reproductive tract including gonads, eyes, and Harderian glands.

Bone marrow was evaluated in sections of sternum, vertebrae, and/or femur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126 200 -/- Male 300 19464 testis seminiferous tubules atrophy moderate V T 8/3/2000 8410773 David Fairchild DB1 1
126 200 -/- Male 300 28048 testis seminiferous tubules mineralization, nos multifocal mild V T 1/29/2001 8780035 Lauri Diehl DB1 1
126 200 -/- Male 300 28048 testis seminiferous tubules atrophy mild V bilateral T 1/29/2001 8780035 Lauri Diehl DB1 1
126 200 +/+ Male 40 15102 thymus NOS NSA V T 5/3/2000 2098350 Unknown Unknown DB1 1
126 200 +/+ Male 40 15111 thymus NOS NSA V T 5/3/2000 2098562 Unknown Unknown DB1 1
126 200 +/+ Female 40 15134 thymus NOS not examined V T 5/3/2000 2098861 Unknown Unknown DB1 1
126 200 +/+ Female 40 15471 thymus NOS NSA V T 5/3/2000 2099200 Unknown Unknown DB1 1
126 200 +/+ Male 300 17438 thymus NOS NSA E F 1/29/2001 8780023 Unknown Unknown DB1 1
126 200 +/+ Male 300 17439 thymus NOS NSA E F 1/29/2001 8780026 Unknown Unknown DB1 1
126 200 +/+ Male 300 19350 thymus NOS NSA V T 8/3/2000 8410522 David Fairchild DB1 1
126 200 +/+ Male 300 22182 thymus NOS NSA V T 8/3/2000 8413113 David Fairchild DB1 1
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Gene ES Cell Line Genotype Gender Age Bin (days) Mouse Organ Organ Structure Finding Distribution Severity Test Validity Comment Test Release Flag Test Date Test Id Scientist Working Set ES Cell Line Order
126 200 +/+ Male 300 28047 thymus NOS NSA V T 1/29/2001 8780092 Lauri Diehl DB1 1
126 200 +/+ Female 300 22193 thymus NOS not examined V T 8/3/2000 8413171 David Fairchild DB1 1
126 200 +/+ Female 300 22193 thymus NOS inflam, chronic moderate V tissue adjacent to thymus T 8/3/2000 8413171 David Fairchild DB1 1
126 200 +/+ Female 300 22995 thymus NOS NSA V T 8/3/2000 8413568 David Fairchild DB1 1
126 200 -/+ Female 40 15118 thymus NOS NSA V T 5/4/2000 2098706 Jill Hagenkord DB1 1
126 200 -/+ Female 40 15469 thymus NOS NSA V T 5/4/2000 2099096 Jill Hagenkord DB1 1
126 200 -/- Male 40 15105 thymus NOS NSA V T 5/2/2000 2098430 Unknown Unknown DB1 1
126 200 -/- Male 40 30903 thymus NOS NSA V T 7/4/2000 21107721 Jill Hagenkord DB1 1
126 200 -/- Female 40 15470 thymus NOS NSA V T 5/2/2000 2099146 Unknown Unknown DB1 1
126 200 -/- Male 300 17436 thymus NOS lymphoid hypoplasia diffuse moderate E F 1/29/2001 8780019 Unknown Unknown DB1 1
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126 200 -/- Male 300 19464 thymus NOS NSA V T 8/3/2000 8410773 David Fairchild DB1 1
126 200 -/- Male 300 22179 thymus NOS lymphoid hypoplasia moderate V T 8/3/2000 8412960 David Fairchild DB1 1
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126 200 +/+ Male 40 15111 thyroid gland NOS not examined V T 5/3/2000 2098562 Unknown Unknown DB1 1
126 200 +/+ Female 40 15134 thyroid gland NOS not examined V T 5/3/2000 2098861 Unknown Unknown DB1 1
126 200 +/+ Female 40 15471 thyroid gland NOS NSA V T 5/3/2000 2099200 Unknown Unknown DB1 1
126 200 +/+ Male 300 19350 thyroid gland NOS NSA V T 8/3/2000 8410522 David Fairchild DB1 1
126 200 +/+ Male 300 22182 thyroid gland NOS NSA V T 8/3/2000 8413113 David Fairchild DB1 1
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